Taiwanese Journal of Obstetrics & Gynecology 56 (2017) 550–553

Contents lists available at ScienceDirect

Taiwanese Journal of Obstetrics & Gynecology

journal homepage: www.tjog-online.com

Case Report

Molecular cytogenetic characterization of a duplication of 15q24.2-q26.2 associated with anencephaly and neural tube defect

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ARTICLE INFO

Article history:
Accepted 2 June 2017

Keywords:
15q24.2-q26.2 duplication
Anencephaly
Neural tube defect
Partial trisomy 15q

ABSTRACT

Objective: We present molecular cytogenetic characterization of a duplication of 15q24.2-q26.2 associated with anencephaly and neural tube defect (NTD).

Case Report: A 35-year-old pregnant woman was found to have a fetus with anencephaly by prenatal ultrasound at 12 weeks of gestation. The pregnancy was subsequently terminated, and a malformed fetus was delivered with anencephaly. Cytogenetic analysis of the cultured placental tissues revealed a karyotype of 46,XX,dup(15) (q24.2q26.2). Parental karyotypes were normal. Array comparative genomic hybridization analysis of the placental tissues revealed a 20.36-Mb duplication of 15q24.2-q26.2 encompassing 100 Online Mendelian Inheritance of in Man (OMIM) genes including *LINGO1*, *MTHFS*, *KIF7* and *CHD2*. Metaphase fluorescence *in situ* hybridization analysis using 15q25.1-specidic probe confirmed a duplication of 15q25.1. Polymorphic DNA marker analysis showed a maternal origin of the duplication.

Conclusion: A duplication of chromosome 15q24.2-q26.2 can be associated with NTD.

Introduction

Neural tube defects (NTDs) such as anencephaly, spina bifida and encephalocele have an incidence of 1–2 per 1000 births which varies with race, geographic variation, socioeconomic classes, nutritional status, and multiple predisposing factors such as single gene disorders of Meckel syndrome, median cleft face syndrome, Roberts syndrome, Jarcho–Levin syndrome and HARD (hydrocephalus, agyria, retinal dysplasia) syndrome, chromosomal abnormalities of trisomy 18, trisomy 13, triploidy and other structural aberrations, teratogens of valproic acid, aminopterin/amethopterin and thalidomide, maternal diabetes, family history, and thermolabile mutation in the *MTHFR* gene [1,2]. Here, we present our experience of molecular cytogenetic characterization of a duplication of 15q24.2-q26.2 associated with anencephaly and NTD.

Case Report

A 35-year-old, gravida 2, para 0, woman was found to have a fetus with anencephaly by prenatal ultrasound at 12 weeks of

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http://dx.doi.org/10.1016/j.tjog.2017.06.003

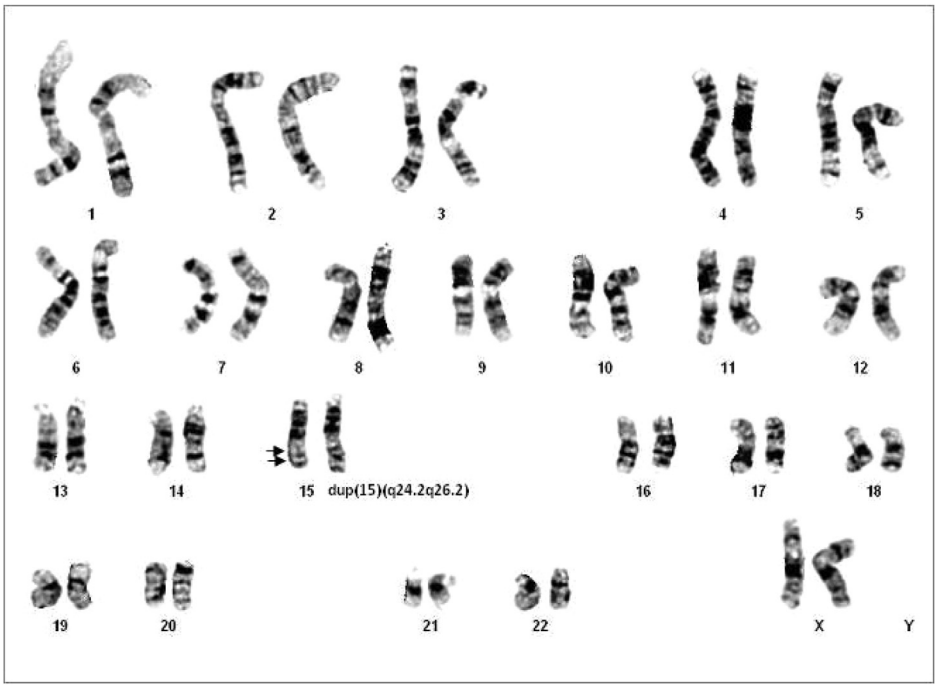

Fig. 1. A karyotype of 46,XX,dup(15) (q24.2q26.2).

gestation. The pregnancy was subsequently terminated, and a malformed fetus was delivered with anencephaly. The woman and her husband were phenotypically normal and did not have diabetes mellitus and any family history of congenital malformations. Conventional cytogenetic analysis of the cultured placental tissues revealed a karyotype of 46,XX, dup(15)(q24.2q26.2) (Fig. 1). The parental karyotypes were normal. Array comparative genomic hybridization (aCGH) analysis of the DNA extracted from placental tissues by SurePrint G3 Unrestricted CGH ISCA v2, 8 × 60 K Array (Agilent Technologies, Santa Clara, CA, USA) revealed a 20.36-Mb duplication of 15q24.2-q26.2 or arr 15q24.2q26.2 (76,350,018–96,715,520) × 3.0 encompassing 100 Online Mendelian Inheritance of in Man (OMIM) genes including *LINGO1*, *MTHFS*, *KIF7* and *CHD2* (Fig. 2). Metaphase fluorescence *in situ* hybridization (FISH) analysis of the cultured trophoblasts using bacterial artificial chromosome (BAC) probes of RP11-962F21 (15q26.1; Texas Red, spectrum red) and RP11-947K12 [15q11.2; fluorescein isothiocyanate (FITC), spectrum green] showed two red signals and one green signal in the dup(15q) chromosome, and one red signal and one green signal in the normal chromosome 15 (Fig. 3). Polymorphic DNA marker analysis by quantitative fluorescent polymerase chain reaction (QF-PCR) assays on the DNA extracted from the placental tissues and parental bloods using the informative markers such as D15S816 (15q25.1) and D15S1514 (15q25.2) determined a maternal origin of the duplication (Fig. 4).

Discussion

The peculiar aspect of the present case is the association of a duplication of 15q24.2-q26.2 with anencephaly and NTD. Lacro et al. [3] first reported a duplication of 15q22.1-qter and a deletion of 13q32.3-qter in an abortus with an omphalocele and a cephalic defect in neural tube closure. Roggenbuck et al. [4] later reported a duplication of 15q24-q26.3 in a female infant with anencephaly. The findings of anencephaly in the present case and the cases reported by Lacro et al. [3] and Roggenbuck et al. [4] indicate the possibility of a gene involved in the neural tube closure being located within 15q24.2-q26.2.

The present case had a 20.36-Mb duplication of 15q24.2-q26.2 encompassing the genes of *LINGO1*, *MTHFS*, *KIF7* and *CHD2*. *LINGO1* (OMIM 609791) is located at 15q24.3 and encodes LINGO1 or LRRN6A protein (leucine-rich repeat protein, neuronal, 6 A). LINGO1 is richly expressed in limbic system and neocortex [5]. LINGO1 is a transmembrane signal protein that inhibits oligodendrocyte differentiation and myelination through intercellular self-interactions [6]. LINGO1 negatively regulates myelination by oligodendrocytes [7,8]. Over-expression of LINGO1 leads to RhoA activation and inhibits oligodendrocyte differentiation and myelination, and loss of Lingo1 confers a neuroprotective effect [8,9]. Mi et al. [10] suggested that blocking LINGO1 as a therapy to promote central nervous system repair. Roetzer et al. [11] reported a family with 15q24 microduplications encompassing *LINGO1* with a broad clinical spectrum including developmental delay, autistic traits and dysmorphic features.

MTHFS (OMIM 604197) is located at 15q25.1 and encodes 5,10-methenyltetrahydrofolate synthetase. Elevated MTHFS expression has been shown to increase folate turnover rate or degradation [12]. MTHFS activity is increased in tumors [13], and *MTHFS* polymorphisms have been associated with congenital malformations such as congenital heart defects and non-syndromic cleft lip and palate [14–16].

KIF7 (OMIM 611254) is located at 15q26.1 and encodes kinesin family member 7. KIF7 plays a role in the hedgehog signaling pathway through the regulation of GLI transcription factor. Mutations in *KIF7* are associated with the autosomal recessive Al-

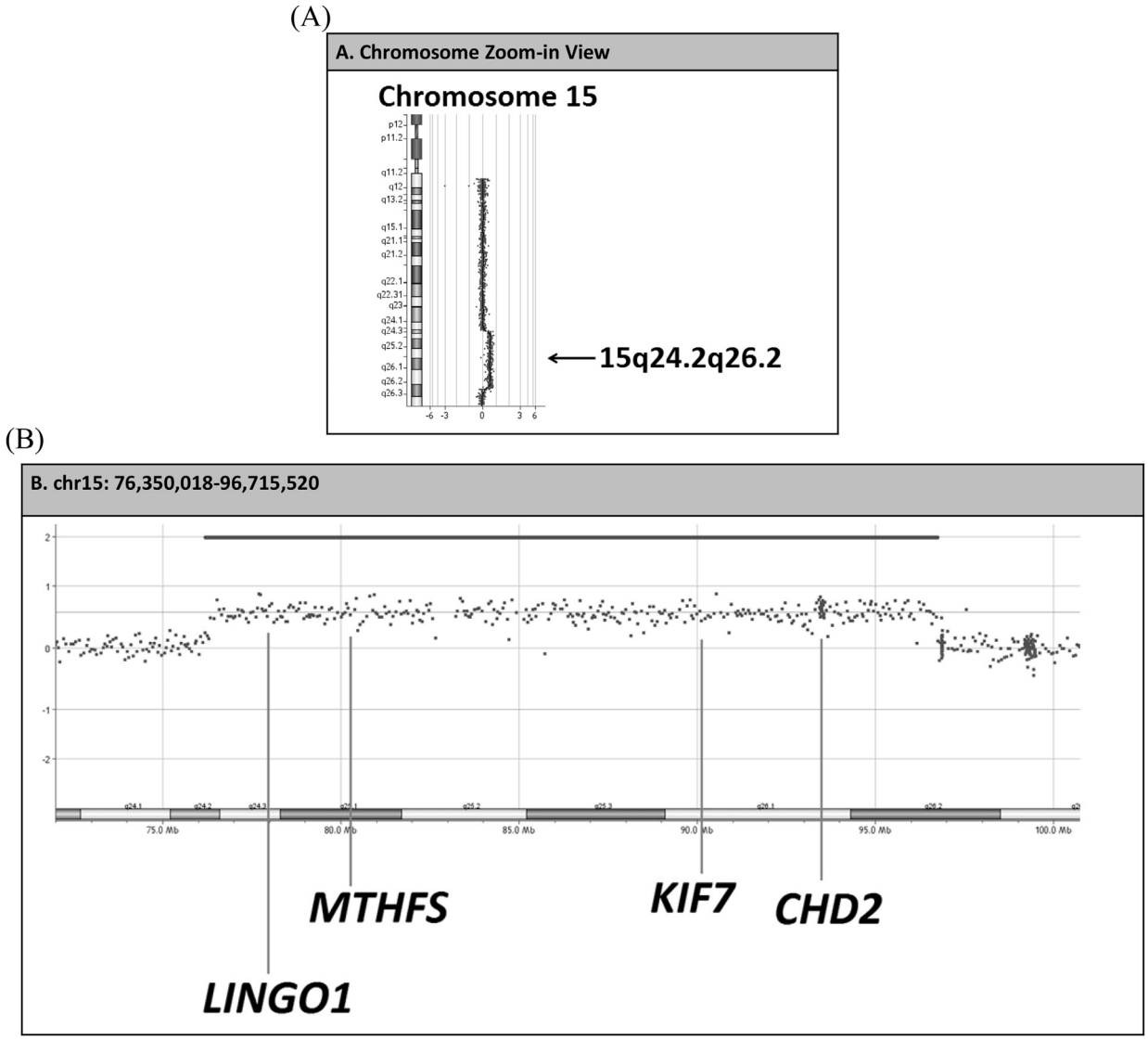

Fig. 2. Array comparative genomic hybridization shows a 20.36-Mb duplication of 15q24.2-q26.2 (A) and (B) chromosome 15 zoom-in views.

Gazali–Bakalinova syndrome (OMIM 607131), hydrolethalus syndrome 2 (OMIM 614120), acrocallosal syndrome (OMIM 200990) and Joubert syndrome 12 (OMIM 200990). Putoux et al. [17] reported homozygous deletion in the *KIF7* gene in two affected members with anencephaly and the other two affected members with hydrocephalus.

CHD2 (OMIM 602119) is located at 15q26.1 and encodes chromodomain helicase DNA-binding protein 2. CDH2 is expressed in the heart, forebrain, extremities, and facial and dorsal regions during embryonic development [18]. Mutations in *CHD2* are associated with autosomal dominant childhood-onset epileptic encephalopathy (OMIM 615369) [19,20]. CDH2 is required for embryonic neurogenesis in the developing cerebral cortex [21].

In summary, we present molecular cytogenetic characterization of a duplication of 15q24.2-q26.2 associated with anencephaly and NTD. Our case provides evidence that a duplication of chromosome 15q24.2-q26.2 can be associated with NTD.

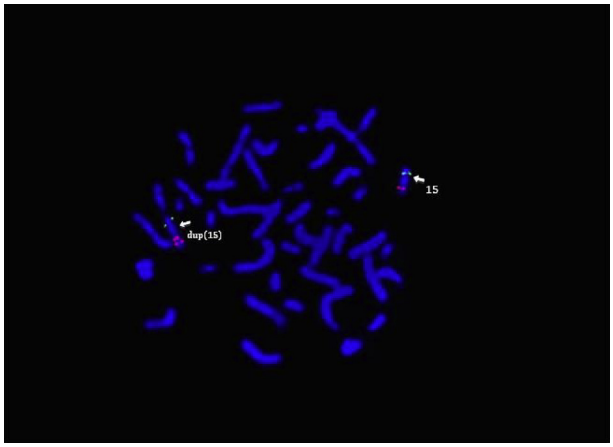

Fig. 3. Metaphase fluorescence *in situ* hybridization analysis using the probes of RP11-962F21 (15q26.1; Texas Red, spectrum red) and RP11-947K12 [15q11.2; fluorescein isothiocyanate (FITC), spectrum green] shows two red signals and one green signal in the dup(15q) chromosome, and one red signal and one green signal in the normal chromosome 15. dup = duplication.

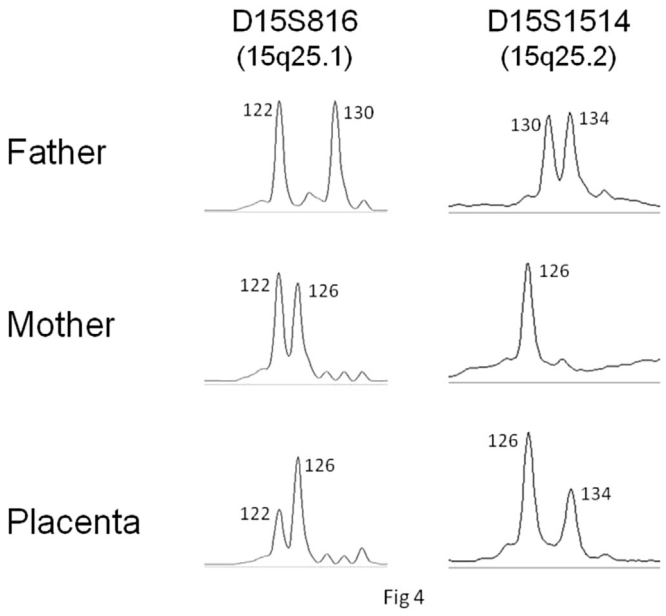

Fig. 4. Polymorphic DNA marker analysis by quantitative fluorescent polymerase chain reaction. assays using the informative markers of D15S816 (15q25.1) and D15S1514 (15q25.2) shows a paternal allele: maternal allele ratio of 1:2 in the placental tissues, indicating a maternal origin of the segmental duplication.

Conflicts of interest

The authors have no conflicts of interest relevant to this article.

Acknowledgements

This work was supported by research grants MOST-104-2314-B-195-009 and MOST-105-2314-B-195-012 from the Ministry of Science and Technology and MMH-E-106-04 from MacKay Memorial Hospital, Taipei, Taiwan.

References

[1] Chen. Chromosomal abnormalities associated with neural tube defects (I): full aneuploidy. Taiwan J Obstet Gynecol 2007;46:325–35.
[2] Chen. Chromosomal abnormalities associated with neural tube defects (II): partial aneuploidy. Taiwan J Obstet Gynecol 2007;46:336–51.
[3] Lacro RV, Jones KL, Mascarello JT, Jones OW, Wilson N, Jones MC, et al. Duplication of distal 15q: report of five new cases from two different translocation kindreds. Am J Med Genet 1987;26:719–28.
[4] Roggenbuck JA, Mendelsohn NJ, Tenenholz B, Ladda RL, Fink JM. Duplication of the distal long arm of chromosome 15: report of three new patients and review of the literature. Am J Med Genet 2004;126A:398–402.
[5] Carim-Todd L, Escarceller M, Estivill X, Sumoy L. *LRRN6A/LERN1* (leucine-rich repeat neuronal protein 1), a novel gene with enriched expression in limbic system and neocortex. Eur J Neurosci 2003;18:3167–82.
[6] Jepson S, Vought B, Gross CH, Gan L, Austen D, Frantz JD, et al. LINGO-1, a transmembrane signaling protein, inhibits oligodendrocyte differentiation and myelination through intercellular self-interactions. J Biol Chem 2012;287:22184–95.
[7] Mi S, Lee X, Shao Z, Thill G, Ji B, Relton J, et al. LINGO-1 is a component of the Nogo-66 receptor/p75 signaling complex. Nat Neurosci 2004;7:221–8.
[8] Mi S, Miller RH, Lee X, Scott ML, Shulag-Morskaya S, Shao Z, et al. LINGO-1 negatively regulates myelination by oligodendrocytes. Nat Neurosci 2005;8:745–51.
[9] Inoue H, Lin L, Lee X, Shao Z, Mendes S, Snodgrass-Belt P, et al. Inhibition of the leucine-rich repeat protein LINGO-1 enhances survival, structure, and function of dopaminergic neurons in Parkinson's disease models. Proc Nat Acad Sci USA 2007;104:14430–5.
[10] Mi S, Pepinsky RB, Cadavid D. Blocking LINGO-1 as a therapy to promote CNS repair: from concept to the clinic. CNS Drugs 2013;27:493–503.
[11] Roetzer KM, Schwarzbraun T, Obenauf AC, Hauser E, Speicher MR. Further evidence for the pathogenicity of 15q24 microduplications distal to the minimal critical regions. Am J Med Genet 2010;152A:3173–8.
[12] Anguera MC, Suh JR, Ghandour H, Nasrallah IM, Selhub J, Stover PJ. Methenyltetrahydrofolate synthetase regulates folate turnover and accumulation. J Biol Chem 2003;278:29856–62.
[13] Field MS, Anguera MC, Page R, Stover PJ. 5,10-Methenyltetrahydrofolate synthetase activity is increased in tumors and modifies the efficacy of antipurine LY309887. Arch Biochem Biophys 2009;481:145–50.
[14] Blanton SH, Henry RR, Yuan Q, Mulliken JB, Stal S, Finnell RH, et al. Folate pathway and nonsyndromic cleft lip and palate. Birth Defects Res A Clin Mol Teratol 2011;91:50–60.
[15] Chowdhury S, Hobbs CA, MacLeod SL, Cleves MA, Melnyk S, James SJ, et al. Associations between maternal genotypes and metabolites implicated in congenital heart defects. Mol Genet Metab 2012;107:596–604.
[16] Li M, Cleves MA, Mallick H, Erickson SW, Tang X, Nick TG, et al. A genetic association study detects haplotypes associated with obstructive heart defects. Hum Genet 2014;133:1127–38.
[17] Putoux A, Thomas S, Coene KLM, Davis EE, Alanay Y, Ogur G, et al. *KIF7* mutations cause fetal hydrolethalus and acrocallosal syndromes. Nat Genet 2011;43:601–6.
[18] Kulkarni S, Nagarajan P, Wall J, Donovan DJ, Donell RL, Ligon AH, et al. Disruption of chromodomain helicase DNA binding protein 2 (CHD2) causes scoliosis. Am J Med Genet 2008;146A:1117–27.
[19] Carvill GL, Heavin SB, Yendle SC, McMahon JM, O'Roak BJ, Cook J, et al. Targeted resequencing in epileptic encephalopathies identifies *de novo* mutations in *CHD2* and *SYNGAP1*. Nat Genet 2013;45:825–30.
[20] Carvill G, Helbig I, Mefford H. *CHD2*-related neurodevelopmental disorders. In: Pagon RA, Adam MP, Ardinger HH, Wallace SE, Amemiya A, Bean LJH, et al., editors. GeneReviews® [Internet]. Seattle (WA): University of Washington, Seattle; 2015 Dec 10. p. 1993–2017. Available at: https://www.ncbi.nlm.nih.gov/books/NBK333201/ [Accessed 2017 March 10].
[21] Shen T, Ji F, Yuan Z, Jiao J. CHD2 is required for embryonic neurogenesis in the developing cerebral cortex. Stem Cells 2015;33:1794–806.